Total synthesis of the reported structure of ceanothine D via a novel macrocyclization strategy†

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The first total synthesis of the reported structure of ceanothine D, a cyclopeptide alkaloid found in red root, was achieved using a highly convergent synthetic strategy. Highlights of the synthesis include the first concomitant macrocyclization and formation of the unique chiral tertiary alkyl-aryl ether bond with complete regio- and stereo-control in the presence of a sensitive Z-enamide moiety to access the strained para-cyclophane present in its structure. This synthetic strategy may be broadly applicable in the generation of other structurally similar cyclopeptide alkaloids, enabling further biological and chemical investigations.

Introduction

Cyclopeptide alkaloids are the most abundant family of natural products isolated from the leaves, stem bark, root bark, and seeds of a wide variety of plant species.† Their role in plants has not been fully elucidated due to lack of availability as yields either from isolation or synthesis are very low. Therefore, development of new synthetic approaches has been an important endeavour since their discovery. The structural similarity of cyclopeptide alkaloids is categorized by the size of the macrocycle that can be 13-, 14-, or 15-membered (Fig. 1). The 14-membered group is the most prevalent, yet most challenging to synthesize because of the enhanced rigidity of the molecule, which results in lack of conjugation between the aromatic ring and the double bond of the enamide moiety.†

Ceanothine D (1) was first reported by Servis from the root bark of Ceanothus americanus (also known as red root or the New Jersey tea plant) along with at least eighteen other cyclopeptide alkaloids that displayed close structural resemblances (Fig. 1). The structure of 1 was proposed based on degradation studies, mass spectrometry, and 1H NMR using a 60 MHz spectrometer.† Interestingly, ceanothine D is the only cyclopeptide alkaloid reported to date to contain the unique chiral tertiary alkyl-aryl ether linkage derived from β-hydroxyisoleucine. The stereochemistry was assigned as L, since it is the most common stereochemical configuration found in nature, and the alkyl-aryl ether stereochemistry was presumed to be R, because most β-hydroxy amino acids in cyclopeptide alkaloids have this stereochemical assignment.†,4 To the best of our knowledge, there is no report of the structural elucidation of the naturally occurring form of ceanothine D or total synthesis of the reported molecule to date.

The use of Ceanothus americanus to treat a wide variety of ailments including blood coagulation and pressure, spleen pain, and even cancer has been supported by its rich history in folk medicine.5,6 In fact, it has been used as a tea substitute during the American Revolutionary and Civil War,5 and it can be accessed as an over-the-counter dietary supplement even today. Although the metabolites of Ceanothus americanus have been of interest to chemists and biologists for many years,6 isolation of individual compounds remains a laborious and difficult challenge since structurally similar cyclopeptide alkaloids are present in varied amounts as complex mixtures.3,7 Furthermore,
Results and discussion

From the retrosynthetic perspective, access to ceanothine D (1) was envisioned through macrocyclization via intramolecular stereocoregulated regioselective azidine ring opening by the phenol group of 2 (Scheme 1). Peptide coupling of acid 5 and free amine of \(L\)-leucineamide followed by subsequent intramolecular Mitsunobu reaction of the resultant amino alcohol would afford 3. Acid 5 could be easily derived from commercially available \(N\)-Boc-\(d\)-serine. The \(Z\)-vinyl iodide moiety of 4 would be constructed by stereoselective olefination of the silyl protected 4-hydroxybenzaldehyde using the Stork–Zhao reagent.24

Starting from commercially available \(N\)-Boc-\(d\)-serine, known precursor 6 was prepared in five steps (Scheme 2).22,23,25 Pinnick oxidation22,23,25 to the corresponding acid 5, followed by EDC-mediated coupling with free amine of \(L\)-leucineamide afforded the amino alcohol 7 in good yield. Mitsunobu cyclization22,23,26 furnishing the desired trisubstituted aziridine (3), and its structure was secured by X-ray crystallographic analysis. Treatment of the TBDPS protected commercially available 4-hydroxybenzaldehyde with the Stork–Zhao reagent23,24 gave the corresponding \(Z\)-vinyl iodide 4 as the major product (see ESI†).

With requisite 3 and 4 in hand, the copper-mediated amidation was examined next. Surveying of current literature revealed the possibility of using catalytic Cu(i)-systems for the formation of \(Z\)-enamides especially in the presence of sensitive functional groups.2,16,26 In particular, utilization of diamine ligands with copper(i) iodide was the most prevalent approach in synthesis of enamide containing complex molecules.22,26,27 Indeed, initial synthetic efforts employing Cu with various diamine ligands in our system led to synthetically significant yields. Size of the diamine ligand27 was crucial in optimizing the yield of the reaction. Switching from sterically less bulky \(N_2N\)-dimethylethylene diamine to \(N_2N\)-dimethyl-1,2-diphenyl-1,2-ethylenediamine27b,c resulted in significantly increased yields,‡ presumably due to suppression of intermolecular aziridine ring opening side reaction(s) of 3 and/or 8 by the diamine ligand.28 The optimized procedure afforded desired \(Z\)-enamide 8 in good yield without any observable epimerization at stereocenters or isomerization of the \(Z\)-vinyl iodide (4). Next, rapid removal of the silyl protecting group furnished linear precursor 2, which was suitably positioned for the key macrocyclization step.

 Gratifyingly, our methodology22 in regio- and stereoselective ring opening of a trisubstituted aziridine translated well into the present intramolecular system despite concerns of creating a strained \(para\)-cyclophane (Scheme 2). To the best of our knowledge, this is the first effective macrocyclization of a 14-membered cyclopeptide precursor with the chemically sensitive \(Z\)-enamide intact. This successful outcome could be attributed...
than the low-resolution $^1$H NMR spectrum structural elucidation. Isolation and extraction from Ceanothus americanus is non-trivial, since extraction methods such as hydrodistillation and a variety of ether fractions are used. The reported structure of ceanothine D remains unknown due to the inaccessibility of natural samples for further analysis and full structure elucidation. The authors declare no conflict of interest.

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Conclusions
In conclusion, the first total synthesis of the reported structure of ceanothine D has been achieved with a novel macrocyclization method in eight steps from a known intermediate 6 (ref. 22b and 25) in overall 8.4% yield. Highlights of the synthesis include the first concomitant, stereocontrolled macrocyclization and formation of the chiral tertiary alkyl-aryl ether bond, particularly in the presence of a chemically sensitive Z-enamide moiety to afford the notoriously strained 1,8-14-membered cyclopeptide alkaloid. The developed strategy may be useful in related research fields as a contribution to the synthetic methods available for the generation of a variety of macrocycles, and will be the goal of future investigations.

Conflicts of interest
The authors declare no conflict of interest.
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Notes and references


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